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Prospective, Randomized Trial of Octreotide to Prevent Pancreatic Fistula After Pancreaticoduodenectomy for Malignant Disease

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Objective
This study was conducted to determine whether the perioperative administration of octreotide decreases the incidence of pancreatic anastomotic leak after pancreaticoduodenectomy for malignancy.

Summary Background Data
Three multicenter, prospective, randomized trials concluded that patients who receive octreotide during and after pancreatic resection have a reduction in the total number of complications or a decreased incidence of pancreatic fistula. However, in the subset of patients who underwent pancreaticoduodenectomy for malignancy, either no analysis was performed or no benefit from octreotide could be demonstrated.

Methods
A single-institution, prospective, randomized trial was conducted between June 1991 and December 1995 involving 120 patients who were randomized to receive octreotide (150 μg subcutaneously every 8 hours through postoperative day 5) or no further treatment after pancreaticoduodenectomy for malignancy. The surgical technique was standardized, and the pancreaticojejunal anastomosis was created using the duct-to-mucosa or invagination technique.

Results
The two patient groups were similar with respect to patient demographics, treatment variables, and histologic diagnoses. The rate of clinically significant pancreatic leak was 12% in the octreotide group and 6% in the control group ($p = 0.23$). Perioperative morbidity was 30% and 25%, respectively. Patients who underwent reoperative pancreaticoduodenectomy had an increased incidence of pancreatic anastomotic leak, whereas those who received preoperative chemoradiation had a decreased incidence of pancreatic anastomotic leak.

Conclusions
The routine use of octreotide after pancreaticoduodenectomy for malignancy cannot be recommended.

Pancreatic anastomotic leak is the most common major complication after pancreaticoduodenectomy. However, in contemporary series, the incidence of pancreatic anastomotic leak or fistula has declined to <20%, and mortality from this complication has decreased to <10%.[1-5] Overall perioperative mortality in patients treated with pancreaticoduodenectomy at large referral centers is now <1%.[3-6] This has caused many surgeons to advocate a more aggressive use of pancreaticoduodenectomy, even for patients with adenocarcinoma of the pancreatic head. However, in such patients, median survival remains <2 years, with only 10% to 20% of patients surviving 5 years.[6] Therefore, treatment-related morbidity must be minimized. For the 10% to 20% of patients who experience a pancreatic anastomotic leak, the morbidity remains significant: their hospital stay is often extended to 1 month or longer, they occasionally require reoperation, they almost always require intravenous hyperalimentation, and they suffer the discomfort and inconvenience of prolonged intraabdominal drain placement.[1,3,5] In patients with cancer, these issues attain even greater significance. Such complications can delay or prevent the delivery of postoperative adjuvant therapy, which has been shown to prolong survival in patients with adenocarcinoma of the pancreatic head.[7] Further, for the patient who experiences early tumor recurrence, the morbidity, time, and expense invested in surgery and a prolonged postoperative recovery make the treatment seem worse than the disease.

There is no consensus on how best to manage the pancreatic stump after pancreaticoduodenectomy. This is best demonstrated by the large number of peer-reviewed articles published on this subject within just the past 5 years.[4,8-14] Virtually every anatomic possibility for anastomosing the pancreatic stump to the jejunum has been proposed, from a single-layer, end-to-end intussuscepting anastomosis[8] to a multilayer anastomosis with a small bowel patch.[9] Factors proposed to decrease complications related to the pancreatic anastomosis include: 1) the use of the duct-to-mucosa technique[4,10]; 2) external drainage of the pancreatic duct with an indwelling stent[11]; 3) decompression of the pancreaticobiliary limb with an external drain,[12] T tube,[3] or transhepatic catheter,[13] with or without Roux-en-Y reconstruction[12]; and 4) the use of fibrin glue biologic adhesive.[9,14] Surgeons' continued problems with the pancreatic anastomosis are further evidenced by recent reports advocating simple closure and drainage with creation of a controlled fistula,[15] injection of the pancreatic duct with Neoprene (Du Pont de Nemours, Italiana, Milan, Italy),[16] and consideration of a second-stage pancreaticojejunostomy in high-risk patients.[17]

An obvious alternative to the development of various surgical techniques for pancreatic reconstruction is to decrease pancreatic exocrine secretion pharmacologically. Somatostatin is a potent inhibitor of pancreatic endocrine and exocrine function.[18] It has been identified in numerous tissues, including the hypothalamus, pancreatic islet D cells, gastrointestinal epithelium, salivary glands, thyroid C cells, and kidney. The synthetic peptide octreotide contains the same amino acid sequences essential to the activity of somatostatin while conferring resistance to enzyme degradation, resulting in a long-acting, stable analog suitable for subcutaneous administration. Octreotide has been shown to rapidly decrease output from, and facilitate closure of, pancreatic cutaneous fistulas.[19,20] These data served as the foundation for studies in Italy and Germany examining the use of octreotide prophylactically in elective pancreatic surgery.[21-23] Each of these trials demonstrated a reduction in the incidence of perioperative complications or pancreatic fistulas in patients who received octreotide. However, the studies involved multiple surgeons who performed many different types of pancreatic resections for both benign and malignant disease; subset analysis of patients who underwent pancreaticoduodenectomy for malignancy either was not performed or failed to demonstrate a benefit from the use of octreotide. We therefore initiated a single-institution, prospective, randomized study to test the hypothesis that perioperative octreotide decreases the incidence of pancreatic anastomotic leak after pancreaticoduodenectomy for malignant disease.

PATIENTS AND METHODS

The study group comprised 120 consecutive patients who underwent pancreaticoduodenectomy for biopsy-proven or suspected malignant disease at one institution from June 1991 to September 1995. Pretreatment evaluation included physical examination, chest radiography, and contrast-enhanced computed tomography (CT). CT

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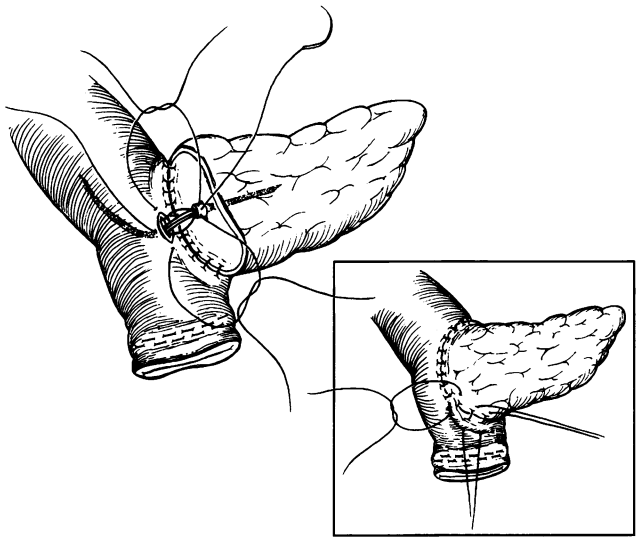

Figure 1. Duct-to-mucosa anastomotic technique for completing the pancreaticojejunal anastomosis.

was performed at 1.5- or 3-mm section thickness and 5-mm scan intervals at the time of intravenous contrast enhancement. Patients were considered for surgery only if they fulfilled objective CT criteria for resectability[24]: 1) no extrapancreatic disease; 2) no evidence of tumor encasement of the superior mesenteric artery or celiac axis, as defined by the presence of a normal fat plane between the tumor and these arterial structures; and 3) a patent superior mesenteric–portal venous confluence. Focal involvement of the superior mesenteric–portal venous confluence did not preclude tumor resection and was treated with segmental venous resection. Forty-six patients received preoperative chemoradiation consisting of external-beam radiation therapy (50.4 or 30.0 Gy) and concurrent continuous-infusion 5-fluorouracil (300 mg/m^2 per day, 5 days/week).[6,25]

All surgical resections were performed using a standard six-step technique, as previously described.[26,27] Pancreaticoduodenectomy included distal gastrectomy in all patients; pylorus preservation was not performed. After tumor resection, electron-beam intraoperative radiation therapy (10 to 15 Gy) was delivered to the bed of the resected pancreas in a dedicated surgery and radiation therapy suite.[28] The intraoperative radiation therapy treatment field extended from the transected bile duct superiorly, to the right kidney laterally, and to the pancreatic remnant medially; the pancreatic remnant was excluded from the treatment field. A standardized pathologic evaluation of the pancreaticoduodenectomy specimen was performed, as recently described.[29]

Gastrointestinal reconstruction was also standardized and involved three basic steps,[27,30] as follows. First, the jejunum was brought retrocolic to the transected pancreas, usually to the left of the middle colic artery. An end-to-side, two-layer pancreaticojejunostomy was performed in all patients over a short (4- to 6-cm), small Silastic stent. One of two techniques for pancreatic anastomosis was used based on the surgeon's intraoperative assessment of the texture of the pancreas and the diameter of the pancreatic duct. If the pancreas was firm and the duct dilated, a duct-to-mucosa technique was used (Fig. 1). If the pancreas was soft or the duct was of normal diameter, the entire cut surface of the pancreas was invaginated into the jejunum (Fig. 2). In both techniques, interrupted 3-0 or 4-0 nonabsorbable sutures were used for the outer layer of the anastomosis; interrupted 4-0 absorbable sutures were used for the inner layer of the duct-to-mucosa anastomosis, and a running 4-0 nonabsorbable suture was used for the inner layer of the invaginating anastomosis. Second, an end-to-side, single-layer choledochojejunostomy was created with interrupted absorbable sutures distal to the pancreaticojejunostomy. Stents were not employed for the biliary anastomosis regardless of the size of the common hepatic duct. In the rare patient who had an indwelling transhepatic catheter, the catheter was transected proximal to the anastomosis and removed 5 to 7 days after surgery. Third, a two-layer, hand-sewn gastrojejunostomy (usually antecolic) was created distal to the choledochojejunostomy. Gastrostomy and jejunostomy tubes were placed in all patients using the Witzel technique. When available, the remaining omentum, based on the greater curvature of the stomach, was placed anterior to the gastrostomy tube in an effort to cover the pancreaticojejunostomy. A 0.25″ closed-suction drain was placed

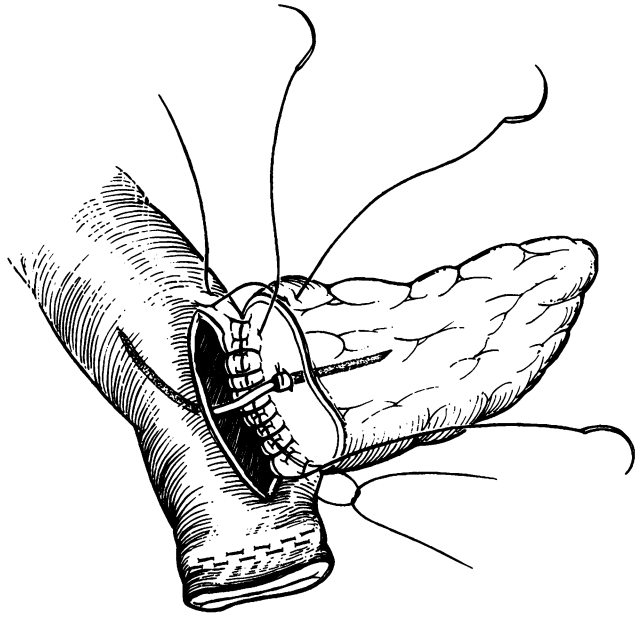

Figure 2. Invagination technique for completing the pancreaticojejunal anastomosis.

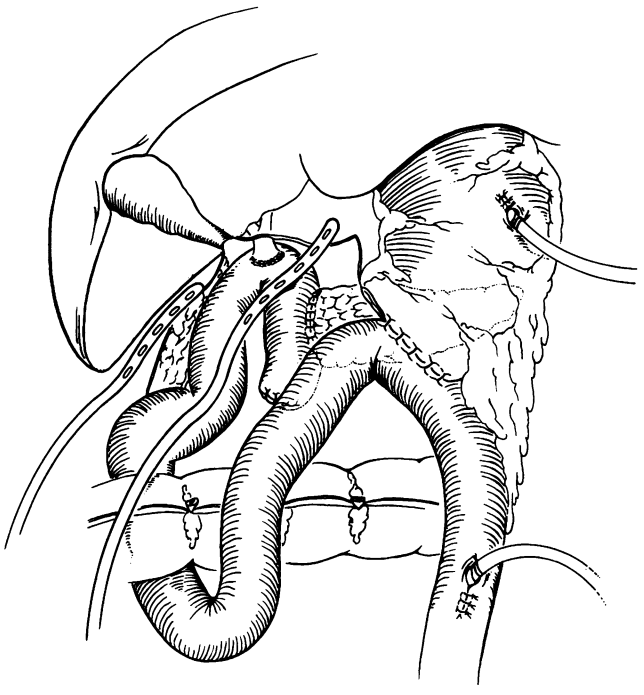

Figure 3. Completed reconstruction after pancreaticoduodenectomy. A gastrostomy tube and a jejunostomy tube were placed in all patients. Two closed-suction drains exited the right abdominal wall. The medial drain was placed close to, but not in direct contact with, the pancreatic anastomosis; the amylase level in the fluid from this drain was recorded beginning on postoperative day 3.

in the vicinity of the pancreaticojejunal anastomosis, but not in direct contact with it (Fig. 3). In patients who were undergoing reoperative pancreaticoduodenectomy, the gastrointestinal reconstruction varied based on the extent of previous surgery, as previously reviewed in detail.[31] However, the technical aspects of anastomotic construction remained unchanged.

At the time of surgery, patients were randomly assigned, based on the number of their medical record, to receive 150 μg of octreotide subcutaneously every 8 hours through postoperative day 5. The initial dose of octreotide was administered either in the operating room after completion of the pancreaticojejunostomy or immediately after surgery, on arrival in the surgical intensive care unit. This schedule of administration was selected based on the rapid onset of action of octreotide: peak serum concentrations are reached within 30 minutes of a subcutaneous dose.[32] The length of treatment was selected in an attempt to obtain the antisecretory effects of octreotide on the pancreas without incurring prolonged delays in the return of gastrointestinal function secondary to octreotide's potent inhibition of gastrointestinal tract motility.[33]

All patients received perioperative intravenous antibiotics with a second-generation cephalosporin for 24 hours (penicillin-allergic patients received ciprofloxacin) and histamine H_2-receptor antagonists during their entire hospitalization. Postoperative enteral feeding was begun on postoperative day 3 using an elemental formula. Enteral feeding was advanced, as tolerated by the patient, under the direction of the nutrition support service. Ice chips and sips of water were allowed on postoperative day 1, and an oral diet was provided beginning on postoperative day 5 (at which time the gastrostomy tube was clamped). Patients then advanced their diet and opened and closed their gastrostomy tubes as desired.

The amylase content of the fluid from the medial abdominal drain (see Fig. 3) was measured and recorded on postoperative day 3. Abdominal drains were removed on or after postoperative day 3 if output was <200 mL per 24-hour period and the amylase content in the drain fluid was normal (as defined by the upper limit of normal for serum amylase). If the drain was not removed on postoperative day 3 because of high output, measurement of the amylase content in the drain fluid was repeated before drain removal. In the absence of a clinical or biochemical pancreatic anastomotic leak (defined below), drains were removed before postoperative day 8. Patients were discharged when independent with ambulation and tolerating clamping of the gastrostomy tube for prolonged periods (8 to 12 hours). All patients were discharged while still receiving jejunostomy feeding, usually administered only at night.

Perioperative (in-hospital or within 30 days of surgery) deaths and complications were recorded. Complications were defined as the need for reoperation, percutaneous drainage of an intraabdominal fluid collection, or transfer to the intensive care unit; the development of a clinical pancreatic anastomotic leak; or a delay in hospital discharge (defined as a hospital stay >21 days). A clinical pancreatic anastomotic leak was defined as the drainage of amylase-rich fluid (>2.5 times the upper limit of normal for serum amylase) in association with fever (>38 C), leukocytosis (white blood cell count >10,000/L), sepsis (hemodynamic instability requiring transfer to the intensive care unit), or the need for percutaneous drainage of an amylase-rich fluid collection. A biochemical pancreatic anastomotic leak was defined as an elevated level of amylase (>2.5 times the upper limit of normal for serum amylase) in the drain fluid on or after postoperative day 3 that was asymptomatic and resolved spontaneously. Patients with clinical or biochemical pancreatic anastomotic leaks were treated with octreotide until the drains were removed, regardless of their initial randomization.

Statistical Analysis

The primary end point of this study was the development of a clinical or biochemical pancreatic anastomotic leak. The population size was determined assuming a total

leak rate (clinical and biochemical) of 30% in the control group and a reduction of the total leak rate to 10% in the octreotide group. To detect a 20% decrease in the leak rate with alpha and beta errors of 5% and 15%, respectively, a total of 108 patients were required. Categorical variables were compared by Student's t test and chi square analysis. Octreotide therapy and variables such as preoperative chemoradiation, reoperative pancreaticoduodenectomy, intraoperative radiation therapy, anastomotic technique, perioperative blood loss, operative time, and tumor histology were assessed for their association with pancreatic anastomotic leak using chi square analysis. Multivariate comparisons were performed using a stepwise regression analysis of variables found to be statistically significant ($p < 0.05$) on univariate analysis.

RESULTS

Patient Characteristics

One hundred twenty consecutive patients were randomized. Ten patients were excluded from analysis because of protocol violations (improper dosing in three, failure to measure drain-fluid amylase in seven); 110 patients were evaluable. Fifty-seven evaluable patients received octreotide and 53 did not (Table 1). There were 57 men and 53 women. The median age was 63 years (range, 29 to 79 years). The two treatment groups were similar with respect to age, tumor type, intraoperative blood loss, anastomotic technique, percentage of patients receiving preoperative chemoradiation and electron-beam intraoperative radiation therapy, and percentage of patients undergoing reoperative pancreaticoduodenectomy. Adenocarcinoma of the pancreas was the most common pathologic diagnosis, present in 58% of the study population (see Table 1).

Table 1. PATIENT DEMOGRAPHICS AND CLINICOPATHOLOGIC FACTORS: NUMBER (%)

Variable	Octreotide Group (n = 57)	Control Group (n = 53)
Gender		
Male	32 (56)	25 (47)
Female	25 (44)	28 (53)
Median age (yr)	63	63
Preoperative chemoradiation		
Yes	26 (46)	20 (38)
No	31 (54)	33 (62)
Intraoperative radiation therapy		
Yes	34 (60)	30 (57)
No	23 (40)	23 (43)
Reoperative pancreaticoduodenectomy		
Yes	10 (18)	11 (21)
No	47 (82)	42 (79)
Anastomotic technique		
Duct to mucosa	42 (74)	40 (75)
Invagination	15 (26)	13 (25)
Histologic diagnosis		
Pancreatic adenocarcinoma	32 (56)	32 (60)
Periampullary adenocarcinoma	13 (23)	7 (13)
Neuroendocrine carcinoma	5 (9)	4 (8)
Other malignant tumors*	6 (11)	6 (11)
Benign†	1 (2)	4 (8)

* Diagnoses included lymphoma, soft tissue sarcoma, recurrent renal cell carcinoma, and locally advanced and recurrent colon carcinoma.
† These patients were taken to surgery for presumed periampullary carcinoma. Pancreatitis was found on permanent-section pathologic analysis.

Effect of Octreotide on Perioperative Mortality and Morbidity

Perioperative mortality and morbidity are summarized in Table 2. The one perioperative death occurred in the one patient in the octreotide group who required reoperation. Before referral, this patient had undergone two previous operations, radiation therapy (both external-beam and intraoperative radiation therapy), and chemotherapy for a localized adenocarcinoma of duodenal origin. A subclinical leak at the pancreaticojejunostomy led to sudden gastroduodenal artery stump blowout approximately 5 weeks after pancreaticoduodenectomy, resulting in exsanguination at the time of emergent reoperation. There were no deaths in the control group, and none of the control patients required reoperation.

Pancreatic anastomotic leak was the most common complication in both treatment arms. The incidence of clinical pancreatic anastomotic leak was 12% (7 of 57) in the octreotide group and 6% (3 of 53) in the control group ($p = 0.23$). The incidence of biochemical anastomotic leak and the combined incidence of biochemical and clinical anastomotic leak did not differ between study groups. Overall, there were no statistically significant differences in either the number or type of complications between the two treatment groups. The median length of hospital stay was 15 days for both groups.

Adverse Effects of Octreotide

No adverse effects could be directly attributed to octreotide. In 6 (11%) of 57 patients treated with octreotide, the hospital stay exceeded 21 days because of delayed return of gastrointestinal function, manifested by poor gastric emptying or intolerance to enteral feeding. None of these patients experienced an infectious intraabdominal complication to account for their delayed hospital discharge. In the control group, 4 (8%) of 53 patients experienced similar complications; the difference between groups was not significant.

Table 2. PERIOPERATIVE MORTALITY AND MORBIDITY: NUMBER (%) OF PATIENTS WITH COMPLICATION

Complication	Octreotide Group (n = 57)	Control Group (n = 53)
Perioperative mortality	1 (2)	0
Anastomotic leaks		
Pancreatic (clinical)	7 (12)	3 (6)
Pancreatic (biochemical)	9 (16)	8 (15)
Pancreatic (total)	16 (28)	11 (21)
Biliary	0	0
Gastric	0	0
Abdominal abscess	3 (5)	2 (4)
Total percutaneous drainage	8 (14)	4 (8)
Reoperation	1 (2)	0
Hospital stay >21 days*	8 (14)	8 (15)
Total patients experiencing 1 or more complications†	17 (30)	13 (25)

* Median hospital stay was 15 days in both groups.
† A complication was defined as a clinical pancreatic anastomotic leak; the need for reoperation, percutaneous drainage of an intra-abdominal fluid collection, or transfer to the intensive care unit; or a hospital stay of more than 21 days.

Factors Associated With Pancreatic Anastomotic Leak

Demographic and treatment variables were examined for their potential association with the development of a pancreatic anastomotic leak (Table 3). When clinical and biochemical leaks were considered (total leaks), preoperative chemoradiation was associated with a decreased incidence ($p = 0.02$) of pancreatic anastomotic leak in univariate analysis. In contrast, reoperative pancreaticoduodenectomy and a histologic diagnosis other than pancreatic adenocarcinoma were associated with an increased incidence of pancreatic anastomotic leak ($p = 0.03$ and $p = 0.01$, respectively).

When clinical anastomotic leak alone was analyzed, the incidence was 5% (3 of 58) after pancreaticoduodenectomy for pancreatic adenocarcinoma, compared with 13% (7 of 52) for patients with other histologic diagnoses ($p = 0.07$). In patients who received preoperative chemoradiation, a clinical pancreatic anastomotic leak occurred in 7% (3 of 46), compared with 11% (7 of 64) for all other patients ($p = 0.43$). Of the variables analyzed, only reoperative pancreaticoduodenectomy was associated with an increased incidence of clinical pancreatic anastomotic leak (24% [5 of 21] versus 6% [5 of 89]; $p < 0.01$). Of the 10 patients who developed a clinical pancreatic anastomotic leak, 5 (50%) had undergone reoperative pancreaticoduodenectomy, 3 in the octreotide group and 2 in the control group.

A stepwise regression analysis was performed to determine the association of total pancreatic anastomotic leak with preoperative chemoradiation, histology, and reoperative pancreaticoduodenectomy. Reoperative pancreaticoduodenectomy remained strongly associated with an increased incidence of total pancreatic anastomotic leak (odds ratio 1.81; $p = 0.03$). Preoperative chemoradiation was again associated with a decreased incidence of leak (odds ratio 0.55; $p = 0.02$). However, the effect of histology on anastomotic leak failed to reach statistical significance ($p = 0.12$).

DISCUSSION

We found no benefit from octreotide in preventing pancreatic anastomotic leak after pancreaticoduodenectomy. These findings are in contrast to the results of three previous randomized trials testing the effect of perioperative octreotide on the incidence of pancreatic anastomotic leaks and overall perioperative complications after pancreatectomy (Table 4). Büchler et al.[21] in 1992 reported on a randomized, double-blind, placebo-controlled, multicenter trial involving 246 patients. Pancreatic fistula was defined as a concentration of amylase *and* lipase in the abdominal drain effluent (single aliquot > 10 mL/day) that was more than three times the serum concentration on or after postoperative day 3, in the absence of clinical or radiographic findings diagnostic of a pancreatic anastomotic leak. Pancreaticoduodenectomy was performed in 200 (81%) of the 246 patients; the other 46 patients underwent other types of pancreatic resection. Pancreatectomy was performed for malignant disease in 139 patients and for chronic pancreatitis in 107. In the 139 patients who underwent pancreatic resection for malignancy, pancreatic fistula occurred in 16 (24%) of the 68 patients who

Table 3. UNIVARIATE COMPARISONS FOR ASSOCIATION OF PANCREATIC ANASTOMOTIC LEAK WITH TREATMENT VARIABLES

Variable	Clinical Leak (p value)	Biochemical Leak (p value)	Total Leaks (p value)
Cell of origin (pancreatic carcinoma *vs.* others)	0.07	0.12	0.01
Preoperative chemoradiation	0.43	0.03	0.02
Reoperative pancreaticoduodenectomy	0.009	0.61	0.03
Intraoperative radiation therapy	0.86	0.61	0.58
Anastomotic technique	0.82	0.24	0.43
Operative blood loss	0.99	0.79	0.82
Operative time	0.35	0.43	0.20

Table 4. RANDOMIZED TRIALS OF PERIOPERATIVE OCTREOTIDE TO PREVENT PANCREATIC FISTULA FOLLOWING PANCREATECTOMY IN PATIENTS WITH MALIGNANCY (PATIENTS WITH PANCREATITIS EXCLUDED)

Reference (year)	Treatment Group	Number of Patients	Dose of Octreotide	Number (%) of Deaths	Number (%) with Complications	Number (%) with Pancreatic Fistula	Median Hospital Stay (days)
Buchler[21] (1992)	Octreotide	68	100 μg SC × 7 days	2 (3)	26 (38)*	16 (24)	29†
	Placebo	71		7 (10)	46 (65)	29 (41)	35†
Pederzoli[23] (1994)‡	Octreotide	76	100 μg SC × 8 days	NA	17 (22)	9 (12)	NA
	Placebo	86		NA	30 (35)	20 (23)	NA
Montorsi[22] (1995)§	Octreotide	111	100 μg SC × 7 days	9 (8)	24 (22)*	10 (9)*	NA
	Placebo	107		6 (6)	39 (36)	21 (20)	NA
Lowy (current study)	Octreotide	57	150 μg SC × 6 days	1 (0.8)	17 (30)	7 (12)	15
	Control	53		0	13 (25)	3 (6)	15

SC = subcutaneously; NA = not available.
* Difference between groups significant at $p < 0.05$.
† Mean hospital stay.
‡ Twelve patients had chronic pancreatitis.
§ Approximately 10% of patients underwent pancreatectomy for benign disease (pancreatitis).

received octreotide compared with 29 (41%) of the 71 patients who received a placebo. In addition, the rate of total complications among patients with malignancy was significantly lower ($p < 0.01$) for the subgroup who received octreotide. These findings prompted the authors to recommend the use of perioperative octreotide, particularly in patients with pancreatic or periampullary carcinoma.

In 1994, Pederzoli et al.[23] published the results of a second placebo-controlled, multicenter trial involving 252 patients. Pancreatic fistula was defined as a concentration of amylase in the drain effluent (>10 mL/day for at least 4 days) that was more than three times the serum concentration on or after postoperative day 4. Pancreaticoduodenectomy was performed in 105 (42%) of the 252 evaluable patients. Pancreatic resection was performed for biopsy-proven or suspected malignancy in 162 patients (12 were found to have pancreatitis on postoperative pathologic evaluation) and for presumed pancreatitis in 90 patients. Of the 162 patients who underwent pancreatectomy for malignancy, only 98 (60%) underwent pancreaticoduodenectomy, a number much lower than one would expect, considering that patients who underwent total pancreatectomy were excluded. In this group of 162 patients, the incidence of pancreatic fistula was 12% among the 76 patients who received octreotide compared with 23% among the 86 patients who received a placebo. Overall, fewer complications were seen in the octreotide-treated patients, but in contrast to the study by Büchler et al.,[21] the difference achieved statistical significance only in patients who underwent pancreatic resection for benign disease. However, the authors did conclude that octreotide treatment reduces the risk of complications associated with pancreatic surgery.

In 1995, Montorsi and colleagues[22] reported the results of a third multicenter study involving 218 patients. In this study, a pancreatic fistula was defined as a concentration of amylase in the drain effluent (>10 mL/day) that was more than three times the serum concentration on or after postoperative day 3. Pancreaticoduodenectomy was performed in 143 (66%) of the 218 evaluable patients. Approximately 90% of patients underwent pancreatic resection for malignancy. The incidence of pancreatic fistula was 9% among the 111 patients who received octreotide and 20% among the 107 patients who received a placebo ($p < 0.05$). In the subset of 143 patients who underwent pancreaticoduodenectomy, however, the incidence of pancreatic fistula was 11% among the 76 patients who received octreotide and 15% among the 67 patients who received placebo; this difference was not statistically significant. Overall, complications were significantly less common in the octreotide group than in the placebo group (see Table 4). Therefore, these authors also supported the use of octreotide in patients undergoing pancreatic surgery.

In contrast to the above three studies, our study in-

Table 5. PATIENTS WHO EXPERIENCED A CLINICAL PANCREATIC ANASTOMOTIC LEAK

Patient Number	Received Octreotide	Reoperative PD	Preoperative Chemoradiation	Anastomotic Technique	Histology	Site of Disease Origin
1	Yes	Yes	Yes	Duct to mucosa	Adenocarcinoma	Duodenum
2	Yes	Yes	No	Duct to mucosa	Islet cell carcinoma	Pancreas
3	Yes	Yes	No	Duct to mucosa	Adenocarcinoma	Pancreas
4	Yes	No	No	Duct to mucosa	Lymphoma	Pancreas
5	Yes	No	No	Invagination	Adenocarcinoma	Pancreas
6	Yes	No	No	Duct to mucosa	Adenocarcinoma	Pancreas
7	Yes	No	Yes	Duct to mucosa	Adenocarcinoma	Bile duct
8	No	Yes	Yes	Duct to mucosa	Islet cell carcinoma	Pancreas
9	No	Yes	No	Duct to mucosa	Sarcoma	Retroperitoneum
10	No	No	No	Invagination	Adenocarcinoma	Ampulla of Vater

PD = pancreaticoduodenectomy.

volved only one operative procedure (pancreaticoduodenectomy) and used a standard operative technique performed at a single institution under the direction of only three faculty surgeons (JEL, PWTP, DBE). All 120 patients were taken to surgery for presumed malignancy; 5 were found to have a benign diagnosis on permanent-section pathologic analysis. The potential impact of the underlying disease on the risk of pancreatic anastomotic leak caused Büchler et al.[21] and Pederzoli et al.[23] to stratify their study populations into two groups, those with malignancy (high-risk) and those with chronic pancreatitis (low-risk). Pancreatic anastomoses are believed to be easier to perform and less likely to leak in patients with chronic pancreatitis because of the firm fibrotic pancreatic remnant and the decreased capacity of the diseased pancreas for exocrine secretion.[21,34] The results from the study by Büchler et al.[21] support this theory: only high-risk patients experienced a decrease in perioperative complications with the use of octreotide. The study by Pederzoli et al.[23] found that the incidence of pancreatic fistula was much lower in patients with pancreatitis (6 of 90 [7%]) than in those with malignancy (29 of 162 [18%]), however, octreotide administration decreased overall complications only in low-risk patients.

Forty-six (42%) of the 110 patients in our study received preoperative 5-fluorouracil–based chemoradiation. Clinical pancreatic anastomotic leaks occurred in 3 (7%) of these 46 patients, compared with 7 (11%) of 64 patients who did not received preoperative chemoradiation (Table 5). None of the three patients who received preoperative chemoradiation and developed clinical pancreatic anastomotic leaks had adenocarcinoma of pancreatic origin, and two of the three underwent reoperative pancreaticoduodenectomy. The three patients include one patient with adenocarcinoma of the duodenum who represents the only perioperative death, a patient who underwent reoperative pancreaticoduodenectomy for neuroendocrine carcinoma, and a patient with adenocarcinoma of the distal common bile duct. The patient with neuroendocrine carcinoma had previously been given multiagent chemotherapy and external-beam radiation therapy for presumed locally advanced adenocarcinoma of the pancreas; the pathologic diagnosis was revised after referral to our institution. The patient with adenocarcinoma of the distal common bile duct underwent rapid-fractionation preoperative chemoradiation and has been previously reported.[35] No patient in this series who underwent protocol-based preoperative chemoradiation for adenocarcinoma of the pancreatic head experienced a clinical pancreatic anastomotic leak.

Ishikawa et al.[36] were the first to suggest that preoperative radiation therapy prevents pancreatic fistula formation after pancreaticoduodenectomy. They reported on 76 patients who underwent pancreaticoduodenectomy between 1983 and 1988. Twenty-two of the 76 patients received 50 Gy of external-beam irradiation before surgery. Pancreatic fistulas developed in 1 (5%) of these 22 patients and in 10 (19%) of the 54 patients who did not receive preoperative irradiation. The authors suggested that radiation therapy decreases pancreatic exocrine function, as indicated by the decreased incidence of fistula and the decreased uptake of [^{75}Se] selenomethionine in the pancreas of patients who had received irradiation.

All patients in our study underwent pancreaticojejunostomy; pancreaticogastrostomy was not performed. A recent randomized trial performed by Yeo et al.[5] at the Johns Hopkins Medical Institutions found no difference in the incidence of pancreatic fistula after pancreaticojejunostomy (11%) or pancreaticogastrostomy (12%). In that study, pancreatic fistula was defined as a radiographically demonstrated leak or an elevated drain-fluid amylase level on or after postoperative day 10. The two strongest predictors for the development of pancreatic fistula were lower patient volume per surgeon and primary ampullary

or duodenal disease. As expected, disease site was significantly correlated with pancreatic texture; soft glands were associated with periampullary tumors arising from the duodenum, ampulla of Vater, or distal common bile duct. Securing sutures is more difficult with a soft pancreatic remnant. In addition, soft glands have been shown to produce significantly more pancreatic juice than firm glands.[34] Although there were no deaths among the patients studied, patients who experienced a pancreatic fistula had a hospital stay of >1 month, and all but one required intravenous hyperalimentation.[5]

In contrast to all previous studies, we separated patients based on whether the pancreatic fistula was present clinically or simply was manifested by a transient elevation in drain-fluid amylase. Because we advocate early removal of abdominal drains, the amylase level in the drain effluent was assessed on postoperative day 3. By definition, patients who were classified as having a biochemical anastomotic leak (or fistula) had no clinical or radiographic findings to support this diagnosis other than an elevation in drain-fluid amylase. These patients all recovered uneventfully and were discharged after a median hospital stay of only 14 days. Of the ten patients who suffered a clinical pancreatic anastomotic leak (Table 5), five had undergone a previous unsuccessful attempt at tumor removal before referral to our institution. The increased technical complexity of reoperative pancreaticoduodenectomy and the associated increases in operative time and blood loss have been reviewed in detail in our two previous publications on this subject.[31,37] However, in this study, operative time and blood loss were not associated with an increased incidence of pancreatic fistula by univariate analysis. Therefore, the reason for the apparent association of reoperative pancreaticoduodenectomy with an increased incidence of pancreatic fistula is unknown. A recent study[38] suggested that perioperative hypothermia delays healing and predisposes patients to infection; this might increase the risk of anastomotic leak. However, our database did not include information on patient core temperature at the time of surgery.

The one death in this series was related directly to a pancreatic anastomotic leak and occurred in a patient who, before referral, had undergone two previous operations, external-beam and intraoperative radiation therapy, and chemotherapy for a localized adenocarcinoma of duodenal origin. Definitive tumor extirpation required *en bloc* resection of the superior mesenteric vein. A subclinical leak at the pancreaticojejunostomy led to sudden gastroduodenal artery stump blowout approximately 5 weeks after pancreaticoduodenectomy, resulting in exsanguination from intraabdominal and gastrointestinal hemorrhage. This patient has been previously reported in detail.[39] The subject of arterial hemorrhage after pancreaticoduodenectomy has been reviewed by Brodsky and Turnbull.[40] They reported five patients, all of whom experienced a sentinel hemorrhage from the gastrointestinal tract or an abdominal drain. Cullen et al.,[1] in their review of the Mayo Clinic experience, also emphasized the high mortality (three of eight patients) seen with hemorrhage in the setting of a pancreatic anastomotic leak. Infection and catheter erosion, if percutaneous drainage is required, can lead to erosion of the stump of the gastroduodenal artery or pseudoaneurysm formation in the hepatic artery. Gastrointestinal or drain tract hemorrhage after the initial 24 to 48 postoperative hours should prompt emergent arteriography. Hepatic artery embolization should be performed if the diagnosis of a pseudoaneurysm is established.

In conclusion, this single-institution, prospective, randomized trial demonstrated no effect of perioperative octreotide on the incidence of pancreatic anastomotic leak after pancreaticoduodenectomy in patients with malignancy. Thus, the routine use of perioperative octreotide in this setting cannot be recommended. The association of pancreatic anastomotic leak with reoperative pancreaticoduodenectomy adds further support to our recommendation that surgeons operate only on patients whose preoperative imaging studies fulfill objective radiographic criteria for tumor resectability. Similar to findings in other recent studies, our incidence of pancreatic anastomotic leak was relatively low, and surgery-related death was rare. However, for the patient who experiences a clinically significant leak, increased morbidity and hospital stay dramatically increase the toxicity of surgical therapy. Therefore, we believe it is reasonable to consider the use of perioperative octreotide in settings where there may be an increased risk for pancreatic leak: reoperative pancreaticoduodenectomy and periampullary tumors of nonpancreatic tumor origin. Finally, based on the favorable outcomes of our patients with biochemical leak treated with octreotide, we recommend the use of octreotide in patients with an elevated drain-fluid amylase level.

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